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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/815,402	03/31/2004	Kimberly F. Fennell	PC25365A	8738

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PFIZER INC.
PATENT DEPARTMENT, MS8260-1611
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EXAMINER	
NASHED, NASHAAT T	
ART UNIT	**PAPER NUMBER**
1656	

DATE MAILED: 06/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/815,402	FENNELL ET AL.	
	Examiner	Art Unit	
	Nashaat T. Nashed, Ph. D.	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-73* is/are pending in the application.

4a) Of the above claim(s) *28-72* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-27 and 73* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/22/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-27 and 73, drawn to a crystal of undecaprenyl pyrophosphate synthase (UPPS), and method of obtaining the crystal, classified in class 435, subclass 193.

II. Claims 28-63, drawn to a method of identifying compounds that bind and inhibit UPPS, classified in class 702, subclass 27.

III. Claims 64 and 65, drawn to a method of solving a crystal form [structure], classified in class 702, subclass 27.

IV. Claims 66-72, drawn to a machine-readable medium and computer, classified in class 700, subclass 90.

The inventions are distinct, each from the other because of the following reasons:

Inventions II and I are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different designs, modes of operation, and effects (MPEP § 802.01 and § 806.06). In the instant case, the different inventions, the crystal of invention I is not used in the method of identifying the compounds that bind or inhibits UPPS.

Inventions III and I are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different designs, modes of operation, and effects (MPEP § 802.01 and § 806.06). In the instant case, the different inventions, the method of invention III does not utilize the crystal of invention I.

Inventions IV and I are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different designs, modes of operation, and effects (MPEP § 802.01 and § 806.06). In the instant case, the different inventions are not disclosed as capable of being used together.

Inventions II and III are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different designs, modes of operation, and effects (MPEP § 802.01 and § 806.06). In the instant case, the different inventions are independent method having different steps and products.

Inventions II and III are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product. See MPEP § 806.05(h). In the instant case, the computer of invention IV can be used in other metods such as that of invention III.

Inventions III and IV are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the

process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product. See MPEP § 806.05(h). In the instant case, the computer can be used in other methods such as that of invention II.

Because these inventions are independent or distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

Because these inventions are independent or distinct for the reasons given above and have acquired a separate status in the art in view of their different classification, restriction for examination purposes as indicated is proper.

During a telephone conversation with Irene Reininger on May 30, 2006 a provisional election was made with traverse to prosecute the invention of Group I, claims 1-27 and 73. Affirmation of this election must be made by applicant in replying to this Office action. Claims 28-72 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

The disclosure is objected to because of the following informalities: "square"-Me at page 16, line 3 appears to be a misprint or undefined abbreviation in the specification.

Appropriate correction is required.

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s). In particular, 37 CFR 1.821, which states:

> (d) Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

Thus, each time there is a reference to amino acid residues from SEQ ID NO: 1, it should be accompanied by SEQ ID NO: 1 (see for example see pages 3, 5, 22 and 23) as well as claim 22.

Claim 2 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 1 is limited to a UPPS in crystalline form. Claim 2 expands the scope of claim 1 to include any composition containing UPPS in any form.

> The following is a quotation of the first paragraph of 35 U.S.C. 112:
> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-27 and 73 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 2, 5, and 8-21 are directed to all possible crystals and co-crystal of UPPS from any biological source and mutants thereof. Claims 3, 4, 6-11, 14, 17-19, and 23-27 are directed to any crystal or co-crystal of any UPPS from any biological source having amino acid sequence homology of 80%, 90% or 100% to SEQ ID NO: 1 bound to any inhibitor which include any substitution, insertion, deletion and combination thereof mutants of SEQ ID NO: 1. Claims 73 is directed to a method of crystallizing UPPS from any *Strptococcocu* under any crystallization conditions using the hanging drop method. The specification, however, only provides a single representative species of these crystals containing only the amino acid sequence of SEQ ID NO: 1, which is an orthorhombic crystal in space group $I2_12_12_1$ with unit cell dimensions a=59.99, b=118.21, and c=178.93. There is no disclosure of any particular relationship between the amino acid sequence of UPPS and the crystallization conditions. The specification has failed to describe any crystal of UPPS of SEQ ID NO: 1 or any other protein that comprises an inhibitor of UPPS.

The court of Appeals for the Federal Circuit has held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula [or] name chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." UC California v. Eli Lilly (43 USPQ2d 1398). For claims drawn to genus, MPEP section 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or physical and/or chemical properties, by functional characteristics

coupled with known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. Also, MPEP section 2163 states that a representative number of species mean that the species, which are adequately described, are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. At the time of invention, the full-length UPPS of SEQ ID NO: 1 was well known in the art along with other UPPS from other bacterial species such as *E.* coli. WO 03/048733 ('733, IDS reference) teaches the crystallization of the protein of SEQ ID NO: 1 and describe identical crystal to that disclosed in the instant application. Also, the crystallization of the *E. coli* enzyme, which has less than 50% sequence homology with SEQ ID NO: 1 is described. While the structure of the *E. coli* UPPS appears to be identical to the structure described in the instant application and in the '733 document, the crystal described by Ko *et al.* (IDS reference) is different, space group $P2_12_12_1$ with unit cell dimension of a 64.18, b=67.33, and c=110.15 obtained under different conditions, see Ko *et al.* J. Biol. Chem. 12/14/2001, 276. 47474-47482, the experimental section and Table 1 at page 47475 and 47476. The instant application describes the crystallization of the same protein that is describe in the WO 03/048733 by document and the formation of an orthorhombic space group $I2_12_12_1$ with unit cell dimensions a=59.99, b=118.21, and c=178.93. In general, for a species of crystal to be adequately and structurally described, the following must be adequately described: (i) the exact chemical composition of the crystal, i.e., the structure feature of all molecules in the crystal including the amino acid sequence of any protein or nucleic acid, (ii) the space group of the crystal; and (iii) the unit cell dimension of the crystal. Clearly, the prior art describes the same crystal taught in the instant application within the experimental errors in the unit cell dimensions. Neither the applicants nor the prior art has described the crystallization of any other UPPS from any other organism with or without a ligand. Thus, the specification fails to describe additional representative species of these crystals by any identifying structural characteristics or properties other than the crystal containing the amino acid sequence of SEQ ID NO: 1 having the cell dimension described at page 17, lines 15 and 16, for which no predictability of structure is apparent. Given this lack of additional representative species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Claims 1-27 and 73 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification does not enable any person skilled in the art to make and use the invention commensurate in scope with these claims. The claims are broader than the enablement provided by the disclosure with regard to all-possible crystals of UPPS or those obtained by the crystallization of a polypeptide having 80%,

90% or 100% sequence homology to SEQ ID NO: 1. Factors to be considered in determining whether undue experimentation is required are summarized *In re* Wands [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim.

The nature and breadth of the claimed invention encompasses any possible crystals comprising any UPPS or 80% or 90% variants of the amino acid sequence of SEQ ID NO: 1, or any crystal obtained from the crystallization of SEQ ID NO: 1 under any conditions and a method of making said crystals. The specification provides guidance and examples in the form of an assay to obtain the protein of SEQ ID NO: 1 and obtain crystal consisting of said protein under specific crystallization conditions at page 17, lines 1-9. While molecular biological techniques and genetic manipulation to make any protein, a general crystallization methods for proteins, and synthetic method to make any compound that binds to UPPS are known in the prior art and the skill of the artisan are well developed, knowledge regarding crystallization of a particular protein and its complexes is lacking. It is well established in the art that obtaining a protein and its complexes in a crystal form is highly unpredictable without any clear expectation of success, and any change in a given crystallization condition including any minor alteration could alter the crystal form and its diffraction characteristics or even lack of crystal formation. It is now evident that protein crystallization is the major hurdle in protein structure determination. For this reason, protein crystallization has become a research subject in and of itself, and is not simply an extension of structure biologist or crystallographer's laboratory. There are many references that describe the difficulties associated with protein crystals. See for example, Gilliland *et* al, (*Curr. Open in Struct. Biol.* 1996, 6, 595-603) in particular page 600, left column second paragraph; Ke *et al.* (Methods, 2004, 34, 408-414); and Wiencek, J. M. (Ann. Rev. Biomed. Eng. 1999, 1, 505-534). Thus, the skilled artesian would be expected to screen large number of crystallization conditions, which may include screening variety of conditions in space, a micro gravity environment. A protein which may crystallize under specific crystallization condition, it mutants or variants may or may not crystallize under the same condition. In many cases, a protein that can't be crystallized, one of its specific mutants might be crystallized. Even if a crystal is obtained, it may or may not be suitable for structure determination by X-ray crystallography. Thus, searching for a crystallization conditions for a protein and its complexes that is suitable for X-ray crystallography is well outside the realm of routine experimentation and predictability in the art of success in is extremely low. The amount of experimentation to identify a crystal for a protein having amino acid sequence homology of 80%-100% of SEQ ID NO: 1, that include insertion, deletion, substitution, and combination thereof mutants and suitable for structure determination X-ray crystallography is enormous. Since routine experimentation in the art does not include identifying proteins and their mutants having UPPS activity, screening large number of crystallization conditions or mutants thereof which can be

crystallized where the expectation of obtaining the desired crystal is unpredictable, the Examiner finds that one skilled in the art would require additional guidance, such as information regarding the amino acid sequences of the UPPS, the chemical structure of a ligand which is binds to UPPS and form the binary complex to be crystallized, and identify a crystallization conditions that produce a crystal suitable for structure determination by X-ray crystallography. Without such guidance, the experimentation left to those skilled in the art is undue.

The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 2, 11-17, 20-22, and 73 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following are the reasons for rejecting the claims:

(a) Claim 2 has at least two interpretations, which render the claim indefinite because the resulting claim does not define the metes and bound of the desired patent protection. Claim 1 is dependent on claim 1 which is directed to UPPS in crystalline form. Claim 2, which depends from claim 1, reads on a composition of the UDDS of claim 1. That is not specifying the composition to be in a crystalline form. For examination purposes, the claim is assumed to be any composition containing UPPS.

(b) Claims 11-17 and 20-22 are not in compliance with the sequence rules, and there fore considered indefinite because the resulting claims do not set forth the metes and bound of the desired patent protection. Claims 11-17, 20, and 21 refer to specific amino acid residues from the specific amino acid sequence disclosed in the sequence listing as SEQ ID NO: 1. Claim 2 refers to UPPS of *S. pneumoniae,* which is disclosed in the specification as SEQ ID NO: 1.

(c) Claim 73 is indefinite because it is a method claim which contains no positive step. Applicant must amend the claim to include positive steps.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:
A person shall be entitled to a patent unless –
(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by

another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 2 is rejected under 35 U.S.C. 102(e) as being anticipated by U. S. patent 6,537,774 ('774, IDS reference).

The '774 patent teaches UPPS of SEQ ID NO:2 from *Streptococcus pneumonia*. The amino acid sequence of SEQ ID NO: 2 of the '774 patent is identical to SEQ ID NO: 1 of the instant application. Also, the patent teaches composition comprising the polypeptide; see column 27, starting on line 28.

Claims 1-25 and 73 is rejected under 35 U.S.C. 102(e) as being anticipated by WO 03/048733 ('733, IDS reference).

The '733 patent document teach the claimed invention. Example 1 of the '733 document starting at page 30 describes the recombinant production of UPPS from *Streptococcus pneumonia* as a fusion protein with His-tag in *E. coli*, and purification of the recombinant protein, and method of measuring UPPS activity. Using the hanging or sitting drop method, example 2 of the '733 document at page 32 teaches two orthorhombic crystals of the native UPPS: (a) space group $P2_12_12_1$ with unit cell dimensions a=59.6, b=118.0, and c=178.2; and (b) space group $I2_12_12_1$ with similar unit cell dimension to the crystal of the first crystal (claim 1-22, and 73). Also, example 2 teaches the same crystals for the complex of UDDP with IPP (claims 23 and 24) as well as a monoclinic crystal in space group $P2_1$ with unit cell dimensions of a=58.1, b=44.6, c=115.5, and beta=98.7 degrees containing a complex of UPPS and FPP (claim 25), see lines 22-32 of page 35.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nashaat T. Nashed, Ph. D. whose telephone number is 571-272-0934. The examiner can normally be reached on MTWTF.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen M. Kerr can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Art Unit 1656